STUDY ON LIPID ABNORMALITIES IN CHRONIC RENAL FAILURE

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CERTIFICATE

This is to certify that this dissertation titled "**STUDY ON LIPID ABNORMALITIES IN CHRONIC RENAL FAILURE"** submitted by **DR.C.SEKAR**. to the faculty of General Medicine, **The Tamil Nadu Dr.M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance

DR. M.KAMARAJ. M.D.,
Professor of Medicine,
Chief, II Medical Unit,
Department of Medicine,
Madurai Medical College,
Madurai.

DR.A.AYYAPPAN, M.D.,
Professor and Head
Department of Medicine,
Madurai Medical College,
Madurai.

DECLARATION

I**, Dr.C.SEKAR** solemnly declare that the dissertation titled "**Study on lipid abnormalities in Chronic Renal Failure"** has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date: **Dr.C.SEKAR**

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CONTENTS

INTRODUCTION

Chronic kidney disease results when a disease process affects the structural or functional integrity of the kidneys. Chronic kidney failure is the result of chronic kidney disease.

Chronic renal disease features various abnormalities of lipid metabolism, which results in an exceedingly atherogenic profile. Although most striking lipid abnormalities are seen in nephrotic syndrome, hyperlipidemia characterizes renal disease of every cause.

Lipid abnormalities in Chronic renal failure are very important, because atherosclerotic heart disease is the foremost cause of morbidity and mortality in patients with end stage renal disease

Cardiovascular diseases are the leading causes of death in end stage renal disease largely as the result of progressively increasing age of ESRD patients and the broad constellation of uremia associated features .

When the kidney function has deteriorated and is no longer adequate to sustain life, renal replacement therapy (RRT), dialysis or transplantation becomes necessary to maintain life. Hence, it is important to prevent the development of chronic renal insufficiency and subsequent

progression to ESRD. Unfortunately kidney disease in its early stages in generally asymptomatic. Early identification of patients at risk for chronic kidney disease is essential. Major risk factors for the development and progression of chronic kidney disease include diabetes, high blood pressure, protein barrier, family history of kidney disease and increasing age. The progression of kidney disease to end stage can be slowed by glycemic control (in diabetes), blood pressure control for the patients with high blood pressure and use of angiotension converting enzyme (ACE) inhibitors.

Cardiovascular disease is the major cause of death among patients with chronic renal failure and ESRD (end stage renal disease). In addition to impairing the microcirculation hypertension may contribute to the development of atherosclerotic coronary artery disease particularly in the presence of many lipid abnormalities observed in end stage renal disease. The patients have reduced HDL-cholesterol and increased plasma triglyceride concentrations and there is defect in the cholesterol transport. Other factors that may contribute to atherosclerotic coronary artery disease in end stage renal disease are reduced HDL-cholesterol synthesis and reduced activity of the reverse cholesterol pathway.

Also, a growing amount of clinical experience data suggests that lipids may be important in the development and progression of chronic renal disease. Potentially injurious lipid abnormalities are invariably present in these patients more likely to progress to end stage renal disease.

So, the analysis of lipoprotein subclass in chronic renal failure patients is very much essential to assess the clinical outcome.

REVIEW OF LITERATURE

LIPOPROTEIN METABOLISM

Lipoproteins are large, mostly spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters), and fat-soluble vitamins through body fluids (plasma, intestinal fluid, and lymph) to and from tissues. They play an essential role in the absorption of dietary cholesterol, long chain fatty acids, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver.

Lipoproteins contain a core of hydrophobic lipids (triglycerides and cholesteryl esters) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids. The plasma lipoproteins are divided into five major classes based on their relative densities: chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL).

Each lipoprotein class comprises a family of particulars that vary slightly in density, size, and migration during electrophoresis, and protein

composition. The density of a lipoprotein is determined by the amount of lipid and protein per particle. HDL is the smallest and most dense lipoprotein, whereas chylomicrons and VLDL are the largest and least dense lipoprotein particles. Most triglyceride is transported in chylomicrons or VLDL, and most cholesterol is carried as cholesteryl esters in LDL and HDL.

The apolipoproteins are required for the assembly and structure of lipoproteins. Apolipoproteins also serve to activate enzymes important in lipoprotein metabolism and to mediate the binding of lipoproteins to cell surface receptors. ApoA-I, which is synthesized in the liver and intestine, is found on virtually all HDL1 particles. ApoA-II is the second most abundant HDL apolipoprotein and is found on approximately two-thirds of all HDL particles.

ApoB is the major structural protein of chylomicrons, VLDL, IDL, and LDL. One molecule of ApoB, either ApoB-48 (chylomicrons) or apoB-100 (VLDL, IDL, or LDL), is present on each lipoprotein particle. The human liver makes only apoB-100, and the intestine makes apoB-48. ApoE is present in multiple copies on chylomicrons, VLDL, and IDL plays a critical role in the metabolism and clearance of triglyceride-rich

particles. Three apolipoproteins of the C-series (apoC-I, -II and -III) also participate in the metabolism of triglyceride-rich lipoproteins.

TRANSPORT OF DIETARY LIPIDS (EXOGENOUS PATHWAY)

Dietary triglycerides are hydrolyzed by pancreatic lipases within the intestinal lumen and are emulsified with bile acids to form micelles. Dietary cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters, respectively.

Longer-chain fatty acids (>12 carbons) are incorporated into triglycerides and packaged with apoB-48, cholesteryl esters, retinyl esters, phospholipids, and cholesterol to from chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is anchored to proteoglycans that decorate the capillary endothelial surfaces of adipose tissue, heart, and skeletal muscle. The triglycerides of chylomicrons are hydrolyzed by LPL, and free fatty acids are released; apoC-II, which is transferred to circulation chylomicrons, acts as a cofactor for LPL in this reaction. The

released free fatty acids are taken up by adjacent myocytes or adipocytes and either oxidized or re esterified and stored as triglyceride. Some free fatty acids bind albumin and are transported to other tissues, especially the liver.

The chylomicrons particle progressively shrinks in size as the hydrophobic core is hydrolyzed and hydrophilic lipids (cholesterol and phospholipids) on the particle surface are transferred to HDL. The resultant smaller, more cholesterol ester-rich particles are referred to as chylomicrons remnants. The remnants particles are rapidly removed from the circulation by the liver in a process that requires apoE.[1].

TRANSPORT OF HEPATIC LIPIDS (ENDOGENOUS PATHWAY)

This one refers to the hepatic secretion and metabolism of VLDL to IDL and LDL. VLDL particles resemble chylomicrons in protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride (~1 mg of cholesterol for every 5 mg of triglyceride). The triglycerides of VLDL are derived predominantly from the esterification of long chain fatty acids.

The packing of hepatic triglycerides with the other major components of the nascent VLDL particle (apoB-100, cholesteryl esters, phospholipids, and vitamin E) requires the action of the enzyme microsomal transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series. The triglycerides of VLDL are hydrolyzed by LPL, especially in muscle and adipose tissues.[1]

As VLDL remnants undergo further hydrolysis, they continue to shrink in size and become IDL, which contain similar amounts of cholesterol and triglyceride. The liver removes approximately 40 to 60 % of VLDL remnants and IDL by LDL receptor-mediated endocytosis via binding to apoE. The reminder of IDL is remodeled by hepatic lipase (HL) to form LDL; during this process, most of the triglyceride in the particle is hydrolyzed and all apolipoproteins except apoB-100 are transferred to other lipoproteins.

The cholesterol in LDL amounts for ~70 % of the plasma cholesterol in most individuals. Approximately 70 % of circulating LDLs are cleared by LDL receptor-mediated endocytosis in the liver. Lipoprotein (a) [Lp(a)] is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional protein called apolipoprotein

(a) [apo (a)]. Apo (a) is synthesized in the liver and is attached to apoB-100 by a disulfide linkage. The mechanism by which Lp (a) is removed from the circulation is not known.

HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT

All nucleated cells synthesize cholesterol but only hepatocytes can efficiently metabolize and excrete cholesterol from the body. The predominant route of cholesterol elimination is by excretion into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported from the plasma membranes of peripheral cells to the liver by an HDL mediated process termed Reverse Cholesterol Transport[1].

Nascent HDL particles are synthesized by the intestine and the liver. The newly formed discodial HDL particles contain apoA-I and phospholipids (mainly lecithin) but rapidly acquire unesterified cholesterol and additional phospholipids from peripheral tissues via transport by the membrane protein ATP-binding cassette protein A **(**ABCA**).** Once incorporated in the HDL particle, cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL. As HDL acquires more cholesteryl ester it becomes

spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDL during lipolysis.

HDL cholesterol is transported to hepatocytes by both an indirect and a direct pathway. HDL cholesteryl esters are transferred to apoB-containing lipoproteins in exchange for triglyceride by the cholesteryl ester transfer protein **(**CETP). The cholesteryl esters are then removed from the circulation by LDL receptor-mediated endocytosis. HD**L** cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class BI (SR-BI), a cell surface receptor that mediates the selective transfer to cells.

HDL particles undergo extensive remodeling within the plasma compartment as they transfer lipids and proteins to lipoproteins and cells. For example, after CETP-mediated lipid exchange, the triglyceride-enriched HDL becomes a substrate for LPL, which hydrolyzed the triglycerides and phospholipids to generate smaller HDL particles.

Transport of endogenous hepatic lipids via VLDL, IDL, and LDL. Note the relative and absolute changes in apoproteins, other than apoB100, as VLDL is converted to IDL and LDL. The sites of action of the two lipases, LPL and HTGL, are denoted.

Transport of exogenously derived lipids from the intestine to peripheral tissues and liver via the chylomicrons system.HDL metabolism and the role of HDL in reverse cholesterol transport. Free cholesterol is accepted from peripheral tissues by HDL_3 and, after esterification, may be transferred to apoB100 lipoproteins.

Physical-Chemical Characteristics of the Major Lipoprotein Classes

Lipoprotein	Density, g/dl	Molecular Mass, kDa	Diameter nm	Lipid %		
				TG	Chol	PL
Chylomicrons	0.95	400×10^3	75-1200	80-95	2-7	3-9
VLDL	0.95-1.006	$10\text{-}80 \times 10^3$	30-80	55-80	5-15	10-20
IDL	1.006-1.019	$5\text{-}10 \times 10^3$	25-35	20-50	20-40	15-25
LDL	1.019-1.063	2.3×10^3	18-25	5-15	40-50	20-25
HDL	1.063-1.210	$1.7\text{-}3.6 \times 10^2$	5-12	5-10	15-25	20-30

The remaining percent composition is made up of the apoproteins.

Note: TG, triglyceride; Chol, the sum of free and esterified cholesterol; PL, phospholipids; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein.

Pathophysiology of Dyslipidemia in CKD and Dialysis:

The spectrum of dyslipidemia in patients with CKD and dialysis patients is distinct from that of the general population. It involves all lipoprotein classes and shows considerable variations depending on the stage of CKD[5]. There seems to be a gradual shift to the uremic lipid profile as kidney function deteriorates, which is further modified by concurrent illnesses such as diabetes[16] and nephrotic syndrome[17]. Apart from quantitative differences major qualitative changes in lipoproteins can be observed, such as oxidization and modification to sdLDL, which render the particles more atherogenic.

Hypertriglyceridemia:

Plasma triglycerides start to increase in early stages of CKD and show the highest concentrations in nephrotic syndrome and in dialysis patients, especially those who are treated with peritoneal dialysis (PD). Plasma triglycerides are predominantly found in two types of lipoproteins in normal individuals. These are chylomicrons, which are assembled in the intestine for the transport of dietary fatty acids,[18-20] and VLDL which are produced in the liver for the transport of endogenous fatty acids. The accumulation of triglycerides is the consequence of both a high production rate and a low fractional catabolic rate. An increased

production of triglyceride rich lipoproteins is possibly a consequence of impaired carbohydrate tolerance and enhanced hepatic VLDL synthesis[21]. The reduced fractional catabolic rate is likely due to the decreased activity of two endothelium associated lipases, namely, LPL and hepatic triglyceride lipase, which have the primary physiologic function of cleaving triglycerides into FFA for energy production or storage. The cause of the decreased lipase activities in uremia is thought to be depletion of the enzyme pool induced by frequent hyalinization in hemodialysis (HD) patients[22], an increase in the plasma apoC-III/apoC-II ratio, and the presence of other lipase inhibitors in plasma. ApoC-II is an activator of LPL, whereas apoC-III is an inhibitor of LPL. The increased apoC-III/apoC-II ratio is usually due to a disproportionate increase in plasma apoC-III[23]. The impaired lipase activities in uremic plasma may also be caused by a decrease in LPL synthesis as a result of secondary hyperparathyroidism or suppressed insulin level [24].

Incomplete catabolism result in the accumulation of remnant particles (chylomicrons remnants and IDL) that contribute to the heterogeneity of the plasma pool of triglyceride-rich lipoproteins with different sites of origin, sizes, compositions[25], and degrees of atherogenicity.[26] These remnants are rich in apoE, a ligand that is critical

for the removal of the particles from the circulation by binding to LPR and perhaps other receptor on the vascular wall[27]. The arterial wall therefore is exposed to high plasma levels of remnant lipoproteins for prolonged durations, which may predispose to atherogenesis.

High Density Lipoprotein:

Patients with CKD generally have reduced plasma HDL cholesterol concentrations compared with nonuremic individuals. Furthermore, the distribution of HDL subfractions are different. Because of the low apo-AI level and decreased LCAT activity[8] the esterification of free cholesterol and hence the conversion of HDL3 to HDL2 are diminished in uremia. This decreased ability of the HDL particles to carry cholesterol leads to an impairment in the reverse cholesterol transport from peripheral cells to the liver, thereby burdening the vasculature with cholesterol and promoting atherosclerosis[28-30].

Another important component of HDL is paraoxonase, an enzyme that inhibits the oxidation of LDL. Plasma paraoxonase activity is reduced in patients with CKD[31], thereby predisposing the LDL and possibly also HDL particles to oxidation. Furthermore infection associated or uremia associated inflammation might convert HDL from

an antioxidant into a pro-oxidant particle[32,33]. All of these may contribute to atherogenesis in CKD.

Apolipoprotein A-IV:

ApoA-IV is a 46-kDa glycoprotein that is synthesized primarily in enterocytes of the small intestine. In vitro studies suggest that apoA-IV might protect against atherosclerosis by promoting several steps in the reverse cholesterol transport pathway, which removes cholesterol from peripheral cells and directs the cholesterol to liver and steroidogenic organs for metabolism[34-36]. Specifically apoA-IV activates LCAT[37,38] and modulates the activation of LPL [39] as well as the protein-mediated transfer of cholesteryl esters from HDL to LDL[40]. Cross sectional studies have shown an inverse relationship between plasma apoA-IV levels and presence of coronary artery disease in the general population[41,42] as well as in patients with CKD.

ApoA-IV has also been identified as a marker of primary CKD, and its plasma levels are already increased when glomerular filtration rate (GFR) is still normal. Furthermore, high plasma apoA-IV concentrations predicted, independent of baseline GFR, the progression of primary nondiabetic kidney disease, defined as doubling of serum creatinine or necessity of renal replacement therapy, during a prospective 7-yr follow-

up study[43]. These findings were unexpected, given the physiologic functions in reverse cholesterol transport and the antioxidative properties of apoA-IV. The high apoA-IV levels[44] that were caused by the impairment of GFR are further modulated by nephrotic syndrome. Specifically, a tubular type of proteinuria cause a decrease in plasma apoA-IV levels. These observations suggest that the human kidney is involved in apoA-IV metabolism, a hypothesis that is further supported by the presence of apoA-IV in kidney tubular cells[45]. In dialysis patients, apoA-IV levels are twice as high as in the general population[46-49].

Low-Density Lipoprotein:

Elevated plasma LDL cholesterol concentration is common in nephritic syndrome but is not a typical feature of patients with advanced CKD, especially those who are on HD. There are, however, qualitative changes in LDL in patients with CKD and dialysis patients. The proportions of sdLDL and IDL, which are considered to be highly atherogenic, are increased sdLDL is a subtype, of LDL that has high propensity to penetrate the vessel wall, becomes oxidized, and triggers the atherosclerotic process. IDL is an intermediate metabolite of VLDL that is normally further degraded to LDL with the cleavage of triglycerides by lipases. Because of decreased hepatic triglyceride lipase

activities in HD patients, the conversion of IDL to LDL is impaired and IDL accumulates [50] in plasma. IDL and sdLDL have high affinity for macrophages, which theoretically promote their entry into the vascular wall to participate in the formation of foam cells and atherosclerotic plaques[51-54]. The plasma levels of apoB, which is the major apolipoprotein of LDL an IDL, are strongly correlated with levels of these lipoproteins.

A vicious cycle has been suggested in uremia in which the decreased catabolism of IDL and LDL leads to their increased plasma residence time and further modification of the apoB contained in these lipoproteins by oxidation, carbamylation, and glycation. These modifications lead to the reduced recognition and binding of these lipoproteins to LDL receptors and LRP in the liver and hence further reduction in plasma clearance by this physiologic pathway. Using stable isotope techniques, it was shown recently that the plasma residence time of LDL and IDL is more than twice as long in HD patients as in nonuremic individuals. This reduced catabolism, however, is masked by the decreased production of LDL, resulting in near normal plasma levels of LDL[55]. In contrast to the decreased clearance by the liver, there is an increased clearance of these altered lipoproteins via the scavenger

pathway. Modified LDL particles, such as ox-LDL and malonodialdehyde-modified LDL, are taken up by macrophages via binding to several cell surface scavenger receptors. The accumulation of cholesterol leads to the transformation of macrophages into foam cells in the vascular wall and contributes to atherogenesis[51-54,56].

Kinetic parameters of apolipoprotein B (apoB) in LDL, apoB in IDL and apolipoprotein(a) [apo(a) in Lp(a). The concentration, production rate, and residence time in plasma are presented for control subjects (light green) and HD patients (dark green). Each bar represents mean $\pm$ SEM. Data for LDL and IDL are derived from reference; data for Lp(a) are derived from reference. Despite differences in the production rate and residence time, there were no statistically significant differences in plasma concentration of the three lipoprotein particles between HD patients and nonuremic control subjects.

Lipoprotein(a):

There is strong evidence that lipoprotein(a) [Lp(a) is a risk factor for CVD in the general population[57,58]. Lp(a) is an LDL-like lipoprotein that consists of apo(a) that is covalently bound to an LDL particle. Apo(a) shows a high homology with Plasminogen and competes with this protein

for binding to Plasminogen receptors, fibrinogen, and fibrin[59]. Plasma Lp(a) concentrations are strongly genetically determined by the apo(a) gene, which contains a heritable number of kringle-IV (K-IV) repeats. The number of K-IV repeats is the basis for the apo(a) K-IV repeat polymorphism[60]. The molecular weight of apo(a) increases with the number of K-IV repeats ranging from 300 to >800 kDa, and is inversely related to the plasma Lp(a) concentration. Thus, individuals with high molecular weight or large apo(a) isoforms have on average low plasma Lp(a) concentrations, whereas those with low molecular weight or small isoforms usually exhibit high plasma Lp(a) concentrations. Depending on the population under investigation, this association explains between 30 and 70% of the variability in plasma Lp(a) levels.

In kidney disease, plasma Lp(a) levels are also influenced by GFR. In patients with large apo(a) isoforms but not those with small apo(a) isoforms, plasma Lp(a) levels begin to increase in stage 1 CKD before GFR starts to decrease. This isoform specific increase in plasma Lp(a) levels was observed in several but not all studies in non-nephrotic patients with CKD and HD patients[49,61-64]. In contrast, in patients with nephrotic syndrome and PD patients[65,66], increase in plasma Lp(a) levels occur in all apo9a) isoform groups, probably as a consequence of the

pronounced protein loss and a subsequently increased production in the liver[67]. After successful kidney transplantation, a decrease in plasma Lp(a) can be regularly observed in HD patients with large apo(a) isoforms and in PD patients with all apo(a) isoform groups[68,69]. Thus, the elevation of Lp(a) in CKD is an acquired abnormality, mostly influenced by the degree of proteinuria and less by the cause of kidney disease[49].

In vivo turnover studies using stable isotope techniques recently elucidated the mechanism for the increased plasma Lp(a) levels in HD patients. The production rates of apo(a) and apoB, the two apolipoproteins that are contained in Lp(a), were normal when compared with control subjects with similar plasma Lp(a) concentrations. The fractional catabolic rate of these apolipoproteins, however, was significantly reduced compared with control subjects. This resulted in a much longer residence time in plasma of almost 9 days for apo(a), compared with only 4.4 days in control subjects. This decreased clearance is likely the result of loss in kidney function in HD patients[71].

Malnutrition and inflammation have also been associated with high plasma Lp(a) levels in HD patients[63,64,72,73]. The elevation of plasma Lp(a), however, can even be observed in patients with normal plasma C-reactive protein and/or normal plasma amyloid A levels[64]. It therefore seems that

inflammation only modifies Lp(a) concentrations but fails to explain the apo(a) phenotype-specific elevation of plasma Lp(a).

In summary, the hallmarks of uremic dyslipidemia are hypertriglyceridemia; increased remnant lipoproteins (chylomicron remnants and IDL); reduced HDL cholesterol; and increased sdLDL, Lp(a), and apoA-IV. Elevated plasma LDL cholesterol level is not typical but can mostly be observed in patients with nephrotic syndrome and PD patients.

Epidemiologic Association between Dyslipidemia and CV Outcome in CKD:

In the general population, high plasma concentrations of LDL cholesterol, low concentrations of HDL cholesterol, and to some extent high total triglyceride concentrations are associated with increased atherosclerotic CV risk[3,4,74]. In the dialysis populations, the preponderance of the literature, including cross-sectional[75-77] and longitudinal studies[78-85], does not support a strong association between dyslipidemia and CVD. This seemingly aberrant relationship may be due, in part, to the approaches of dyslipidemia assessment. The precise contributions of lipids to atherogenicity should probably be evaluated

longitudinally using multiple measurements overtime, because the plasma lipid patterns change substantially as kidney disease progresses, as illustrated by the decline of plasma LDL levels from the nephrotic stage to the HD stage. Furthermore, the atherogenic potential of dyslipidemia in CKD may depend more on the apolipoprotein than on lipid abnormalities and may not always be recognized by measurement of plasma lipids alone, as suggested by Attman and Alaupovic[75]. An additional caveat is that, in many dialysis patients, CVD is caused or accentuated by other risk factors, such as volume overload, medial calcification, and arrhythmogenicity, and may not necessarily be related to atherosclerosis.

Total Cholesterol:

In large administrative databases, the relationship between plasma total cholesterol and mortality in HD patient has been found to be U-shaped[87,88]. The group with total cholesterol between 200 and 250mg/l had the lowest risk for death, whereas those with levels >350mg/dl had a relative risk of 1.3 fold and those with levels <10mg/dl had a relative risk of 4.2-fold. The association between low total cholesterol and increased mortality, however, was reduced after statistical adjustment for plasma albumin levels. Subgroup analysis provides further insights into the potential effects of plasma total cholesterol on clinical outcomes. A

recent study of 1167 HD patients found that among those with low plasma albumin level (3.5 to 3.9g/dl), low plasma total cholesterol levels were also associated with increased all cause mortality. Among those with plasma albumin >4.5g/dl, however, high plasma total cholesterol levels were associated with increased mortality (10, as observed in the general population. This dichotomous relationship was confirmed in the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, which showed a nonsignificant negative association of cardiovascular mortality with plasma total as well as non-HDL cholesterol levels in the presence of inflammation and/or malnutrition; in contrast, there was a positive association between total and non-HDL cholesterol and mortality in the absence of inflammation or malnutrition. These observations are compatible with the hypothesis that the inverse association of total cholesterol levels with mortality in dialysis patients is mediated by the cholesterol lowering effect of malnutrition and/or systemic inflammation and not due to a protective effect of high cholesterol concentrations.

IDL Cholesterol:

In observational studies, high plasma IDL cholesterol levels have been shown to be a risk factor independent of LDL cholesterol for coronary artery disease in the general population and may also be a

predictor for aortic atherosclerosis in HD patients[90]. As discussed, IDL cholesterol is often elevated in uremia. Unfortunately, the current clinical assays do not differentiate between LDL cholesterol and IDL cholesterol. Therefore, current clinical assays may not accurately asses the atherosclerotic burden of plasma cholesterol in uremia.

Lp(a) Concentrations and Apo(a) Polymorphism:

The association of Lp(a) with atherosclerotic complications has been investigated in numerous studies in dialysis patients. The results were inconsistent in prospective as well as in retrospective studies. This inconsistency might have been due, at least in pat, to the nonstrandardized assay method for Lp(a) in the past. When apo(a) phenotyping was performed in conjunction with plasma Lp(a) concentrations, however, an association between the apo(a) K-IV repeat polymorphism and CV complications was consistently observed. A cross sectional study in 607 HD patients showed an association between low molecular weight apo(a) phenotype with history of coronary events. Two large prospective studies also found a clear association of the apo(a) polymorphism with coronary events and total mortality, respectively. Kronenberg et al. followed 440 HD patients for 5 yr and found a strong association between the low molecular weight apo(a) phenotype and severe coronary events. In contrast, plasma Lp(a) in those with clinical

events showed only a trend toward elevated levels and did not reach statistical significance. Similarly, the CHOICE Study recently reported small apo(a) isoforms to be associated with total mortality in an inception cohort of >800 incident dialysis patients who were followed for a median of 33.7 mo. In that study, Lp(a) concentrations were associated with CV events but not with total mortality.

Apolipoproteins:

In the general population, plasma apoA-IV was reported to be lower in patients with CVD compared with control subjects, and this association was independent of HDL cholesterol and triglyceride concentrations. Similarly, participants in the Mild to Moderate Kidney Disease Study with CVD complications also had lower apoA-IV levels than those without. More data in various stages of CKD are required to confirm these findings.

Hyperlipidaemia and Progression of Kidney Disease:

It has long been suggested that hyperlipidaemia could cause renal injury and contribute to the progression of renal disease[7,110]. There have been a number of observational studies showing that lipid abnormalities are associated with a reduction in kidney function in the general

population. It is uncertain if it is the lipid abnormalities that cause the reduction in kidney function or if impaired renal function or proteinuria itself cause both the lipid abnormalities and reduction in renal function[13,14]. Most studies have been small and a meta-analysis of these studies to assess the effect of lipid reduction on the progression of renal disease has shown than lipid reduction may preserve GFR and reduce proteinuria. More recent studies have shown that HMG-CoA reductase inhibitors (statins) can reduce proteinuria and slow the decline in renal function. The effect of statins in reducing the decline in GFR was more significant in patients with proteinuria[91-94].

Furthermore, it has been well established that proteinuria contributes to the progression of renal disease[91,95]. Despite optimal medical management with interventions to achieve tight blood pressure[96] and blood glucose control[97], the use of angiotension converting enzyme (ACE) inhibitor[98] and angiotension II[99] receptor blocker (ARB) or combined therapy[100], patients with renal failure are at risk for progressive deterioration of their renal function. Statins have been shown to reduce proteinuria and delay the rate of progression of renal disease in patients with proteinuria and hypercholesterolaemia[92,93]. These benefits are in addition to the effects of ACE inhibitor and ARB. However, recent data

have suggested that statins have effects beyond lipid reduction and may have a beneficial anti-inflammatory effect in patients with normal or low cholesterol levels[101,102]. In addition to their lipid-lowering effects, statins can influence important pathways that are involved in the inflammatory and fibrogenic responses, which are commonly associated with many forms of progressive renal injury such as reduction in TGF-β production and inhibition of the proliferative actions of platelet-derived growth factor[103,104].

Finally, statins can decrease coronary events in patients without cardiovascular disease[105,106] and also reduce the mortality rates in patients with pre-existing coronary artery disease. Even for those with serum cholesterol levels as low as 3.5mmol/L and in diabetics without coronary artery disease or high cholesterol, statins have been demonstrated to be beneficial[107,108]. In patients with moderate CKD (GFR of 30 to 59.99mL/min per 1.73m^2) statins have been demonstrated to reduce the incidence of cardiovascular events[109].

Lipids in Nephrotic Syndrome:

Disturbed lipoprotein metabolism is a consistent feature of the nephrotic syndrome (NS). The development of this form of secondary

dyslipidemia appears to be independent of the underlying renal disease and may substantially contribute to the increased cardiovascular risk that has been observed in these individuals as well as to the progression of renal failure. The most common lipid abnormalities in patients with NS are elevated concentrations of total and LDL-cholesterol as well as a predominance of cholesterol depleted small, dense LDL particles. However, in a considerable number of cases, elevated concentrations of triglycerides (due to accumulation of VLDL and remnant lipoproteins such as intermediate density lipoprotein (IDL)) can also be observed. In addition, individuals with nephrotic range proteinuria exhibit increased concentrations of Lp(a) that, in contrast to what is usually noticed in CKD patients without proteinuria, is not phenotype-specific. This means that most patients with the NS have Lp(a) concentrations that are substantially elevated compared with controls of the same apo(a) isoform. Finally, HDL-cholesterol levels have variously been reported to be increased, decreased, or normal in subjects with nephrosis.

The degree of hyperlipidaemia corrates directly with severity of the proteinuria and inversely with the serum albumin. As reduced GFR is by itself associated with hyperlipidaemia the strong and independent correlation between proteinuria and reduced GRF also increases the risk

of hyperlipidaemia and proteinuria. Conversely, proteineria has an inverse correlation with the level of HDL, cholesterol. These risk factors likely predispose patients with nephrotic syndrome to an increased risck or coronary artery disease.

Among nephrotic patients, lipoprotein abnormalities were similar between diabetics and non-diabetic patients in a small study and both groups have elevated (TG), LDL and VLDL cholesterol and low HDL cholesterol. However, patients with diabetic CKD have lipoprotein abnormalities that are a reflection of renal insufficiency similar to that of patients with renal insufficiency due to other causes. These abnormalities however may be further accentuated by the diabetes and the abnormal metabolic control.

Lipids in Hemodialysis and Peritoneal Dialysis:

Dialysis is very effective for the amelioration of uremic symptoms and certain features of uremic toxicity. The initiation of renal replacement therapy as well as the choice of dialysis modality may also influence the phenotypic characteristics of uremic dyslipidemia in patients with ESRD. however, the lipid and apolipoprotein profile that characterizes predialytic renal failure remains essentially unchanged during long-term

hemodialysis (HD). Thus, HD patients usually display increased concentrations of intact or partially metabolized triglyceride rich lipoproteins, reduced serum levels of HDL cholesterol and elevated concentrations of Lp(a). Total and LDL cholesterol values are within normal limits or reduced in this patient population, whereas the subfractionation of apolipoprotein B-containing lipoproteins usually reveals a predominance of small, dense LDL particles. The pathophysiological mechanisms that underlie the alterations in lipoprotein metabolism in HD patients are generally similar with those described in predialysis renal failure individuals. However, the dialysis procedure may result in additional defects in lipid homeostasis (such as increased catabolic rate of apolipoprotein AI) that reinforce the clinical expression of these mechanisms.

Dyslipidemia in kidney transplants:

Dyslipidemia, alone or as part of the metabolic syndrome, is an established risk factor for CVD mortality in kidney transplant recipients. The main causes are thought to be steroids, calcineurin inhibitors[9-12], sirolimus, Diuretics and Betablockers.

About 60 % of kidney transplant recipients have total cholesterol level greater than 240 mg/dL (6.21 mmol/L); about 35 % have hypertriglyceridemia. Low level of high density lipoprotein cholesterol (<35 mg/dL [0.91 mmol/L]) occur in about 15 % kidney transplant[15] recipients- - a percentage similar to that in the general population. The concentrations of lipoprotein (a) and small, dense LDL-C, which are atherogenic, is increased.

Lipid Management in CKD Patients Stages 3 to 4 (GFR 15 to 50 ml/min/1.73 m^2)

The NKF and National Cholesterol Education Program Adult Treatment Panel (ATP) III offer similar guidelines for the management of dyslipidemia in patients with CKD; however, significant differences exist.In the NKF recommendations, CKD is regarded as a CHD risk equivalent and an annual lipid panel is recommended. As with any dyslipidemic patient, a comprehensive search for secondary causes of dyslipidemia should be conducted, including a search for endocrine disorders such as hypothyroidism and diabetes and medications such as corticosteroids, protease inhibitors, beta-blockers, diuretics, and estrogen.

Elevated LDL-C

Although patients with CKD frequently have multiple abnormalities in their lipid profile, LDL-C reduction is the primary goal of therapy. The NKF recommends LDL-C < 100 mg/dl for patients with CKD. Currently the NKF does not recommend a more aggressive LDL goal for patients with CKD and symptomatic atherosclerotic disease. Based on the amended ATP III guidelines, it might be prudent to treat to an LDL goal of < 70 mg/dl in patients with CKD with atherosclerotic disease. As in the general population, statins are the cornerstone of therapy for dyslipidemia. Treatment with a statin in conjunction with therapeutic lifestyle changes is usually required to obtain these goals. All statins can be used safely in patients with CKD; however, differences in the pharmacokinetic properties give some statins a safety advantage in patients with advanced CKD (GFR < 30 ml/min/1.73 m^2). Because the excretion of atorvastatin in the kidneys is negligible, no dose adjustment for reduced GFR or hemodialysis is required. If combination therapy with a gemfibrozil is likely, then fluvastatin may be the safest choice. Other statins require dose adjustments as CKD becomes more advanced.

In patients not at their LDL goal on atorvastatin or fluvastatin, ezetimibe or bile acid sequestrants can be added safely. Bile acid sequestrants' safety may be limited by their tendency to increase triglycerides, which frequently are elevated in CKD. In addition, bile acid

sequestrants may be limited by their tendency to bind to other medications and reduce their absorption.

Mixed Dyslipidemia

Most patients with CKD have triglyceride as well as HDL abnormalities along with elevated LDL (mixed dyslipidemia). After LDL goal attainment, non-HDL should be the primary goal in the management of patients with CKD with mixed dyslipidemia. Non-HDL is the only lipid measurement that correlates positively with cardiovascular mortality in hemodialysis patients. Very-low-density lipoprotein and intermediate-density lipoprotein are both known to be elevated in patients with CKD with mixed dyslipidemia, and therefore non-HDL may be a better marker of atherogenic cholesterol levels. Based on NKF recommendations, patients with CKD should be treated to an LDL-C < 100 mg/dl and a non–HDL-C < 130 mg/dl.

Patients with mixed dyslipidemia frequently require combination therapy with a statin plus additional lipid-lowering drugs that could include ezetimibe, a fibrate, niacin, or omega-3 fatty acids. Although ezetimibe has a negligible effect on HDL and triglycerides, the addition of ezetimibe to a statin results in a significant additional reduction in non–HDL-C, which is the secondary therapeutic goal in mixed

dyslipidemia . The combination of ezetimibe and a statin is relatively safe and well tolerated in patients with CKD

The omega-3 fatty acids may also be used in combination with a statin. Although published data on this combination in patients with CKD is limited, omega-3 fatty acids do not have significant interactions with statins and do not require dose reductions for impaired renal function.

Although fibrates can be used to treat mixed dyslipidemia, they need to be used carefully, because they are predominantly metabolized by the kidneys. According to the NKF guidelines, gemfibrozil is the fibrate of choice in patients with CKD. There is still controversy concerning the safety of fenofibrate in patients with CKD, because of its propensity for increasing serum creatinine and homocysteine to a greater degree than gemfibrozil. Due to the increased risk of rhabdomyolysis with fibrate and statin therapy in patients with CKD, the combination requires more vigilant monitoring, and patients need to report muscle symptoms immediately. Combined with a statin, fenofibrate clearly has advantages due to its lack of pharmacokinetic interactions with statins and lower propensity for rhabdomyolysis.[1] When gemfibrozil is selected for combination treatment with a statin, consideration should be given to changing the statin to fluvastatin, for which there is no pharmacokinetic

interaction and fewer cases of rhabdomyolysis have been reported compared with other statins. Because of fluvastatin's lower efficacy in LDL reduction, the addition of a third drug, ezetimibe, may be necessary . Because CKD alone is a risk factor for rhabdomyolysis, the combination of a statin with any fibrate still needs to be weighed carefully from a risk-benefit perspective.

Niacin is also an option for the treatment of mixed dyslipidemia. Niacin has been shown to increase HDL-C, and reduce both lipoprotein (a) and triglycerides, which are elevated in patients with CKD, but its use is limited due to poor tolerability. The NKF clinical practice guidelines recommend reducing niacin dosing by 50% for GFR < 15 mg/ml/1.73 m^2. Bile acid sequestrants are usually not an option in mixed hyperlipidemia, due to their tendency to increase triglycerides.

Very High Triglycerides (> 500 mg/dl)

The first goal for patients with fasting triglycerides > 500 mg/dl is to prevent pancreatitis. Fibrates are frequently started in this scenario, because they are better tolerated than niacin and are more efficacious triglyceride-lowering drugs than the statins. Currently, because of safety concerns, gemfibrozil would be recommended over fenofibrate . Although some studies suggest that the dose of gemfibrozil does not need

to be reduced in severe renal failure, the NLA Safety Task Force on Lipid-Lowering Drugs recommends that the gemfibrozil dose should be reduced to 600 mg/day for patients with a GFR < 60 ml/min/1.73 m^2 and avoided in patients with a GFR < 15 ml/min/1.73 m^2. Finally, if fenofibrate must be used, the dose should not exceed 48 mg/day and creatinine levels should be monitored carefully.

Another option for very high triglycerides is to treat with omega-3 fatty acids derived from fish oil. The main active ingredients in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic (DHA). Four grams of omega-3 fatty acids per day, in the form of fish oil capsules, have been shown to reduce triglycerides 35% to 45%. The omega-3 fatty acids are safe in patients with CKD and have minimal drug interactions. Until recently, a major limitation was that over-the-counter preparations had only 200 to 300 mg omega-3 fatty acids per capsule, requiring the consumption of 12 to 16 capsules/day. The only available prescription-brand omega-3 fatty acid contains almost 900 mg omega-3 fatty acids, requiring only 4 capsules/day.

Lipid Management in Hemodialysis Patients (CKD Stage 5; GFR < 15 ml/min/1.73 m^2)

The options for hemodialysis CKD stage 5 patients are more limited than patients with CKD stages 1 through 4. For patients with

elevated LDL-C, choosing statins with limited renal excretion, such as atorvastatin or fluvastatin, may be more important . In mixed dyslipidemia, omega-3 fatty acids may have a more prominent role, because the NLA recommends avoiding fibrate use in patients with a GFR < 15 ml/min/1.73 m^2. In patients with very high triglycerides, clinicians can treat with 3 to 4 g/day omega-3 fatty acids, or if a fibrate must be used then gemfibrozil can be given at a reduced dose of 600 mg/day.

Proposed Treatment Algorithm for Lipid Management in Patients With CKD (Stage 3 to 5)

Lipid Disorder	**Therapeutic Option**
Moderate to severe CKD, stages 3 to 4 (GFR 15–59 ml/min/1.73 m^2)	
Elevated LDL-C	1. Atorvastatin, add ezetimibe if not at LDL-C goal 2. Fluvastatin, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia* (not at non-HDL† goal)	1. Atorvastatin or fluvastatin + ezetimibe 2. Fluvastatin + gemfibrozil 600 mg/day + ezetimibe if not at non-HDL goal 3. Statin + omega-3 fatty acids, add ezetimibe if not at non-HDL goal 4. Statin + fenofibrate 48 mg/day, add ezetimibe if not at non-HDL goal
Very high triglycerides (triglyceride ≥500 mg/dl)	1. Gemfibrozil 600 mg/day 2. Omega-3 fatty acids 3–4 g/day 3. Fenofibrate 48 mg/day

CKD stage 5 (hemodialysis or GFR <15 ml/min/1.73 m^2)	
Elevated LDL-C	Atorvastatin (10–80 mg/day) or fluvastatin 40 mg/day, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia	Atorvastatin or fluvastatin 40 mg/day, add ezetimibe 10 mg/day or omega-3 fatty acids 3–4 g/day if not at non-HDL goal
Very high triglycerides	Omega-3 fatty acids 3–4 g/day or gemfibrozil 600 mg/day

AIMS AND OBJECTIVES

- To study the Lipid abnormalities in patients with Chronic renal failure.

MATERIALS AND METHODS

Setting:-

Chronic renal failure patients admitted in medical wards of Govt. Rajaji Hospital, Madurai.

Collaborating departments

1. Department of Nephrology

   Madurai Medical College, Madurai.

2. Department of Bio Chemistry

   MMC, Madurai.

Design of the Study : Cross sectional Study

Period of Study : From February 2008 to July 2008

Sample Size : 25- controls

56-Chronic renal Failure Patients(study cases)

Definitions:

Chronic Kidney disease:

It is defined by the presence of kidney damage or decrease in kidney function (Glomerular filtration ratio < 60 ml/mt/1.73m^2) for the three months or more, irrespective of the etiology.

Kidney damage:

It is defined as structural or functional abnormalities of kidney, initially without decreased GFR. Kidney damage can be diagnosed by any abnormalities in the blood (elevated blood urea and creatinine) urine (proteinuria, granular casts), imaging study or by biopsy.

Kidney Failure:

It is defined as either level of GFR decreased to <15ml/min, which is accompanied in most cases by signs and symptoms of uremia or a need for initiation of kidney replacement therapy (dialysis or transplantation) for treatment for complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity.

End stage renal failure (ESRD) is defined as a level of GFR to <5ml/min where survival is not possible without renal replacement therapy.

GFR is the best estimate of kidney function. The serum creatinine alone is not at accurate measure of the glomerular filtration rate. Creatinine is secreted by the renal tubules and as the renal function worsens the amount secreted increases.

GFR can be estimated using the cockcroft – Gault formula[2]

$$\text{CrCL (ml/mt)} = \frac{\text{140-age x weight (kg)}}{\text{72 x S.creatine (mg/dl)}} \text{ x 0.85 (for women)}$$

Dyslipidemia:

Any abnormality in plasma lipoprotein concentration or composition that is associated with an increased risk for atherosclerotic cardiovascular disease.

Lipid profile:

Plasma level of total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides.

Inclusion criteria:

1. **Clinical**

Anaemia of chronic renal failure

Hypertension

Uremic symptoms – Three months duration

2. **Biochemical**

    a. Elevated blood urea & serum creatinine

3. **Ultra sonographic**

    a. Contracted kidney

    b. Increased cortical echogenicity

    c. Loss of cortico medullary differentiation

Exclusion criteria:

Patients with chronic renal failure with the following conditions were excluded from this study.

1. Diabetes mellitus
2. Nephrotic syndrome
3. Obesity BMI >30
4. Liver disease
5. Alcohol abuse / smokers
6. Thyroid dysfunction
7. Taking steroids, diuretics (Thiazides), beta blockers.
8. Oral contraceptive pills

9. Lipid lowering drugs.

These patients were evaluated on the basis of the proforma on the following guidelines

- Clinical history and physical examination
- Routine investigations like blood HB%, total count, differential count, blood sugar, urine analysis.
- Renal parameters inducting blood urea, serum creatinine.
- Fasting lipid profile
- ultrasonogram abdomen .

All specimens were analyzed within 4 to 6 hours of collection. Total cholesterol and triglycerides in the plasma were measured enzymatically and then the cholesterol in the supernatant is measured after precipitation of APO-B containing lipoprotein to determine the HDL cholesterol. LDL cholesterol is estimated by using the friedewald formula.

FRIEDEWALD FORMULA appears to be the most practical & reliable method for determining LDL-cholesterol in clinical practice.

LDL-Cholesterol=Total cholesterol-[HDL-C+(Triglycerides/5)]

VLDL is estimated by dividing the plasma triglycerides by 5 reflecting the ratio of cholesterol to triglyceride in VLDL particles. This formula is reasonably accurate if test resolution is obtained on fasting plasma and if the triglyceride level is less than 350mg/dl. The accurate determination of LDL-C level in conditions with triglyceride levels greater than this requires application of ultra centrifugation techniques (BETA QUANTIFICATION)

Ethical Committee approval	:	Obtained
Consent	:	Informed consent was obtained
Financial support	:	Nil
Conflict of interest	:	Nil

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2002).**

Using this software, range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference

between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

Table 1 : Age distribution

Age group	Cases		Controls	
	No.	**%**	**No.**	**%**
41-45 years	1	1.8	4	16
46-50	29	51.8	12	48
51-55	19	33.9	5	20
55-59	7	12.5	4	16
Total	56	100	25	100
Range	45-57		41-59	
Mean	51.2		50.4	
S.D.	3.0		4.9	
'p'	**0.1536** **Not significant**			

The mean age of the patients were 51.2 years and maen age of the controls were 50.4 years.There was no significant difference between the study cases and controls in the age(p value 0.153).Hence they are comparable.

Table 2 : Sex distribution

Sex	Cases		Controls	
	No.	%	No.	%
Male	28	50	10	40
Female	28	50	15	60
'p'	**0.7945** **Not significant**			

There was no significant difference between study group and controls regarding the sex distribution (p value0.7945).Hence they are comparable.

Table 3 : BMI

BMI	Cases	Control cases
Range	22-26	22-26
Mean	24.55	24.76
S.D.	1.08	1.09
'p'	**0.3668** **Not significant**	

The mean BMI of study cases was 24.55 Kg/m^2 and that of controls was 24.76 Kg/m^2 .There was no significant difference between the study group and controls in this parameter.Hence they are comparable.

Table 4 : Lipid Profile

Lipid	Cases			Controls			'p'
	Range	Mean	S.D.	Range	Mean	S.D.	
TC	158-269	213.6	14.9	132-245	207.8	22.1	**0.1761 Not Significant**
TGL	110-264	205.9	44.9	112-180	148.0	16.3	**0.0001 Significant**
HDL	16-75	39	18.5	38-86	60.7	14.3	**0.0001 Significant**
LDL	110-171	139.4	16.4	110-172	127.2	15.6	**0.1031 Not Significant**

TOTAL CHOLESTEROL

The mean total cholesterol in the study population was 213.6 mg/dl and in the control group it was 207.8 mg/dl. There is no statistically significant difference between the serum cholesterol levels of cases and controls.(p value 0.1761).

TRIGLYC ERIDES

The mean triglyceride in study group was 205.9 mg/dl and 148 mg/dl in control group. There is significant difference between the two groups as suggested by the p value 0.0001.

HDL CHOLESTEROL

HDL in our study showed a significant reduction in CRF cases compared with controls. The mean HDL in cases were 39 mg/dl and 60.7 mg/dl in controls. The difference was statistically significant with a p value of 0.0001.

LDL CHOLESTEROL

LDL Cholesterol was high in cases compared to controls, but the difference was not significant statistically. The mean LDL in cases was 139.4 mg/dl and 127.2 mg/dl in controls. The p value was 0.1031(Not significant).

DISCUSSION

Chronic kidney disease results when a disease process affects the structural or functional integrity of the kidneys. Chronic kidney failure is the result of chronic kidney disease. Cardiovascular disease is a major cause of mortality in patients with mild to moderate chronic kidney disease and end stage renal disease. Dyslipidemia has been established as a well known traditional risk factor for cardiovascular disease in general population and it is well known that patient with CKD exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipdemia.

This study was done to identify the lipid abnormalities that occur in CRF patients admitted in Govt. Rajaji Hospital, Madurai.

A total of 56 cases who fulfilled the diagnostic criteria for CRF were included in the study. 25 age, sex and BMI matched healthy controls who fulfilled the inclusion and exclusion criteria were taken for comparing the lipid profile.

Among 56 cases the mean age was 51.2 yrs with the range of 45 – 57 yrs The mean age of controls was 50.4 yrs and range was 41 – 59 yrs.

There was no significant difference between cases and controls with regard to the age. (P value – 0.1536). So they can be compared.

There were equal number of males and females in the study group, 28 males and 28 females. Among the 25 controls, 10 were males and 15 were females. There was no significant difference between cases and controls as far as sex is concerned. (P value – 0.7945)

The mean BMI of the cases was 24.55 kg / m2 .The mean BMI of the controls was 24.76 kg / m2. There was no significant difference between cases and controls with respect to BMI.

On analyzing the lipid profile and comparing the CRF cases with controls we found that there is significant increase in triglycerides and significant decrease in HDL–cholesterol. The change in total cholesterol and LDL-C between cases and controls was not significant.

TOTAL CHOLESTEROL:

The mean total cholesterol in the CRF cases was 213.6 mg/dl and that of the controls was 207.8 mg/dl. There was no statistically significant difference in this parameter. (P value – 0.1761).This observation was similar to the results obtained by E.Kimak and

coworkers in their work on plasma lipoproteins in CRF patients. They also concluded that total cholesterol is not increased significantly in patients with CRF[114].

TRIGLYCERIDES:

Significant increase in serum triglycerides was seen in cases when compared with controls. Mean triglycerides was 205.9 mg in cases and 148 mg / dl in controls.(P value is 0.0001). This result was in concordance with the work done by E.Kimak and team, in which they demonstrated significant increase in Triglycerides, LDL and Apo-B concentrations[114].In another study, done by Bhagwat.R , Joshi S P and team, they concluded that CRF patients were having marked triglyceridemia of 232 mg / dl as compared to controls.(P value less than 0.01) [111].Another Indian study on dyslipidemia in patients with CRF and renal transplantation by B.Shah, S.Nair and coworkers they demonstrated that triglycerides was elevated significantly in CRF patients on conservative management[117].These results shows that hypertriglyceridemia is an important lipid abnormality in patients with CRF.

LDL CHOLESTEROL:

Our study demonstrated an increase in LDL cholesterol between cases and controls. (139.4 mg/dl vs 127.2 mg / dl). This was not significant statistically.p value(0.1031). This was similar to the study by Bhagwat R and Joshi S P where they found that LDL cholesterol in CRF patients showed an increase compared to controls which is not statistically significant[111]. Study by E.Kimak and team showed results not comparable to our study. LDL cholesterol showed significant increase among CRF patients compared with controls in their study[114]. Although the total concentrations of LDL are not significantly increased there is predominance of small dense particles which are particularly susceptible to oxidation in CRF. These small particles are thought to be more atherogenic than larger LDL substrates[112].

HDL CHOLESTEROL :

Our study demonstrated a significant decrease in HDL in CRF cases when compared with controls (39mg/dl vs 60.7mg/dl (Pvalue 0.001). This was in concordance with the results obtained by Bhagwat R and team where they found HDL cholesterol to be significantly low. (20 +/- 11)mg/ dl(P value less than 0.001) in CRF groups[111]. Patients with CKD generally have reduced plasma HDL cholesterol concentrations when compared with non uraemic individuals.

CONCLUSIONS

1. Lipid abnormalities is common in CRF.
2. Total cholesterol changes are not statistically significant.
3. Triglycerides shows statistically significant increase in CRF cases when compared with normal.
4. LDL – C is increased in CRF patients but it is not statistically significant when compared with controls.
5. HDL – C shows a statistically significant decrease in CRF patients compared with controls.

SUMMARY

Dyslipidemia is a fairly common occurrence in CRF patients. Cardiovascular mortality in patients with CRF is related to dyslipidemia. This study was done to identify the lipid abnormalities and its significance in CRF patients by comparing with age, sex and BMI of matched healthy control population.

After institutional ethical clearance with an informed consent and with inclusion and exclusion criteria, 56 cases of CRF were taken as study cases and Three fasting lipid profile were estimated. 25 age, sex and BMI matched healthy Population were taken as controls. The data were entered in master sheet and analyzed statistically.

Dyslipidemia is seen in CRF patients. The total cholesterol, even though it was high in CRF cases compared with controls, but the change was not significant statistically. Triglycerides showed a statistically significant increase in CRF cases. LDL-C was elevated in CRF cases but the change was not significant statistically. HDL-C on the other hand showed a statistically significant drop compared to controls. These lipid abnormalities may be an important contributing factor to the cardiovascular mortality in patients with CRF.

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PROFORMA

Name	Age	Sex
IP Number	Occupation	Address

Presenting complaints

Oliguria

Pedal edema

Nausea,vomiting

Pruritus

Hiccups

Facial puffiness

Dyspnea

Past history

Diabetes

Hypertension

TIA

Stroke

Drug history

Thiazides,Beta blockers,Steroids

Family history

H/o Diabetes,Hypertension,Hyperlipidemia

Personal history

Smoking,Alcoholism

General examination

Pallor Icterus Cyanosis Clubbing LNE

Pedal edema Facial puffiness JVP

Evidence for hyperlipidemia

Xanthelasma Arcus Tendinous or Eruptive xanthoma

Vitals

Pulse BP RR Temp Fundus

CVS

RS

Abdomen

CNS

Investigations

Urine

Albumin,Sugar,Deposits

24 hour urine protein

Blood

Sugar

Hb,TC,DC

Renal function tests

Blood Urea

Serum creatinine

USG abdomen for kidney size

Fasting lipid profile

Total cholesterol,HDL,LDL,Triglycerides

FINAL DIAGNOSIS

APPENDIX IV

ABBREVIATIONS

ACE	–	Angiotensin converting enzyme
ATP	–	Adult treatment panel
ARB	–	Angiotensin receptor blocker
BMI	–	Body mass index
CETP	–	Cholesteryl ester transfer protein
CKD	–	Chronic kidney disease
CRF	–	Chronic renal failure
ESRD	–	End stage renal disease
GFR	–	Glomerular filtration rate
HD	–	Hemodialysis
HDL	–	High density lipoprotein
HL	–	Hepatic lipase
IDL	–	Intermediate density lipoprotein
LDL	–	Low density lipoprotein
LCAT	–	Lecithin cholesterol acyl tranferase
LPL	–	Lipoprotein lipase
MTR	–	Microsomal transfer protein
NS	–	Nephrotic syndrome
PD	–	Peritoneal dialysis
RRT	–	Renal replacement therapy
TC	–	Total cholesterol
TGL	–	Triglycerides
VLDL	–	Very low density lipoprotein

APPENDIX II

MASTER CHART CASES

sl no	sex	age	BMI	sugar	urea	creatinine	Creatinine clearance	TC	TGL	HDL	LDL
1	M	50	25	98	102	2.2	34	246	223	26	146
2	F	48	25	102	108	2.2	35	234	212	28	154
3	F	51	26	113	90	28	36	221	239	25	148
4	F	53	26	90	102	2.9	37	224	215	30	151
5	M	50	26	94	94	2.6	34	211	219	32	145
6	M	54	25	115	88	2.3	35	219	206	23	155
7	F	49	26	102	92	2.3	37	229	218	26	159
8	F	50	23	95	75	2.9	36	227	233	30	150
9	F	56	24	110	106	2.7	38	247	218	61	142
10	M	50	25	97	94	2.5	34	234	245	27	158
11	F	57	24	114	70	2.8	35	230	240	25	157
12	M	48	24	106	80	2.2	40	196	110	60	114
13	M	54	25	84	74	2.5	41	217	147	71	117
14	M	47	26	90	85	2.1	39	221	144	62	130
15	F	56	23	105	76	2.9	38	240	138	65	148
16	F	50	25	108	79	2	40	225	150	70	125
17	M	47	25	110	81	2.8	41	214	127	71	118
18	F	56	25	116	78	2	38	220	136	64	129
19	F	50	25	98	90	2.7	40	211	155	70	110
20	M	52	26	100	78	2.7	39	223	140	75	120
21	M	48	25	106	75	2.2	37	255	241	64	143
22	M	50	23	111	72	2.9	41	227	151	72	125
23	F	49	25	98	80	2.8	40	239	147	60	130
24	F	54	24	107	83	2.6	38	220	154	61	134
25	F	54	25	107	83	2.8	36	225	149	60	150

26	F	50	23	90	89	2.6	39	209	140	67	114
27	M	54	24	118	128	5.6	14	237	258	20	164
28	M	48	22	115	124	4.2	15	237	244	22	154
29	F	50	25	88	126	4.4	16	224	237	24	154
30	M	53	24	94	114	4.1	17	225	235	26	145
31	F	57	26	108	118	5.2	14	233	236	25	161
32	M	49	25	111	123	5.7	15	230	226	27	157
33	F	50	25	120	135	4.5	16	221	223	28	148
34	M	57	25	97	127	4.2	14	227	243	19	160
35	F	51	24	114	119	3.9	15	232	237	29	156
36	F	49	25	80	103	3.9	16	222	244	25	148
37	M	51	24	94	106	3.9	17	217	227	27	145
38	F	50	25	110	123	5.2	14	231	223	24	163
39	F	56	26	108	119	4	15	241	234	23	171
40	M	49	26	102	115	5	15	235	258	22	161
41	M	50	25	120	122	4.8	16	232	237	26	150
42	M	48	24	106	124	6.9	8	216	248	38	129
43	M	54	24	110	130	9.4	6	199	246	30	120
44	F	50	25	94	118	6.8	9	158	148	38	118
45	F	46	23	112	134	12.6	6	218	264	34	131
46	M	51	22	118	164	12.6	5	183	260	16	115
47	M	55	24	88	130	10.6	5	201	254	24	126
48	F	52	22	99	144	7.5	8	187	152	41	116
49	M	54	24	108	160	11.8	6	195	240	20	127
50	M	50	23	118	132	16	5	212	238	30	135
51	M	52	24	84	115	10.5	7	209	230	31	132
52	M	45	25	104	158	13.6	6	219	236	30	140
53	F	50	24	116	148	13.8	5	218	246	32	137
54	F	46	26	84	126	7.7	9	179	156	28	120
55	F	54	25	96	134	8.5	8	228	196	34	135
56	M	53	24	102	128	6.6	9	209	156	64	114

MASTER CHART CONTROLS

sl no	sex	age	BMI	sugar	urea	creatinine	Creatinine clearance	TC	TGL	HDL	LDL
1	M	59	25	105	21	0.8	105	220	125	60	147
2	F	48	26	98	28	0.6	106	208	136	74	118
3	F	59	26	87	19	0.7	111	226	158	70	125
4	M	53	25	80	22	0.6	109	221	144	85	157
5	M	48	23	76	26	0.8	107	132	128	65	112
6	F	46	22	78	21	0.7	109	183	134	55	128
7	F	55	25	98	24	0.8	111	208	150	72	114
8	M	49	23	116	25	0.9	112	222	170	86	122
9	M	56	25	94	29	0.8	110	209	145	76	124
10	F	46	26	112	32	0.8	107	197	154	72	115
11	F	51	24	108	28	0.7	113	209	140	64	127
12	F	41	24	105	32	0.7	114	212	158	70	126
13	F	48	24	88	25	0.8	112	200	180	64	110
14	F	46	24	96	26	0.8	107	203	142	80	115
15	F	52	25	94	64	1.2	109	232	154	40	156
16	F	47	25	108	68	0.9	110	238	150	44	114
17	M	50	26	102	70	1	112	232	155	47	154
18	M	48	26	88	78	1.1	113	200	143	40	110
19	F	44	24	90	72	1.3	113	245	176	38	172
20	M	47	25	76	56	1.2	114	197	112	47	128
21	F	43	24	84	64	0.9	115	205	144	51	126
22	F	51	25	110	58	1.3	105	202	168	49	120
23	F	50	25	102	60	0.7	105	183	154	53	130
24	M	50	26	94	60	1	111	209	124	61	124
25	M	45	26	88	48	1	110	203	155	54	118

KEY TO MASTER CHART

BMI - Body mass index (Kg/m^2)

TC - Total cholesterol (mg/dl)

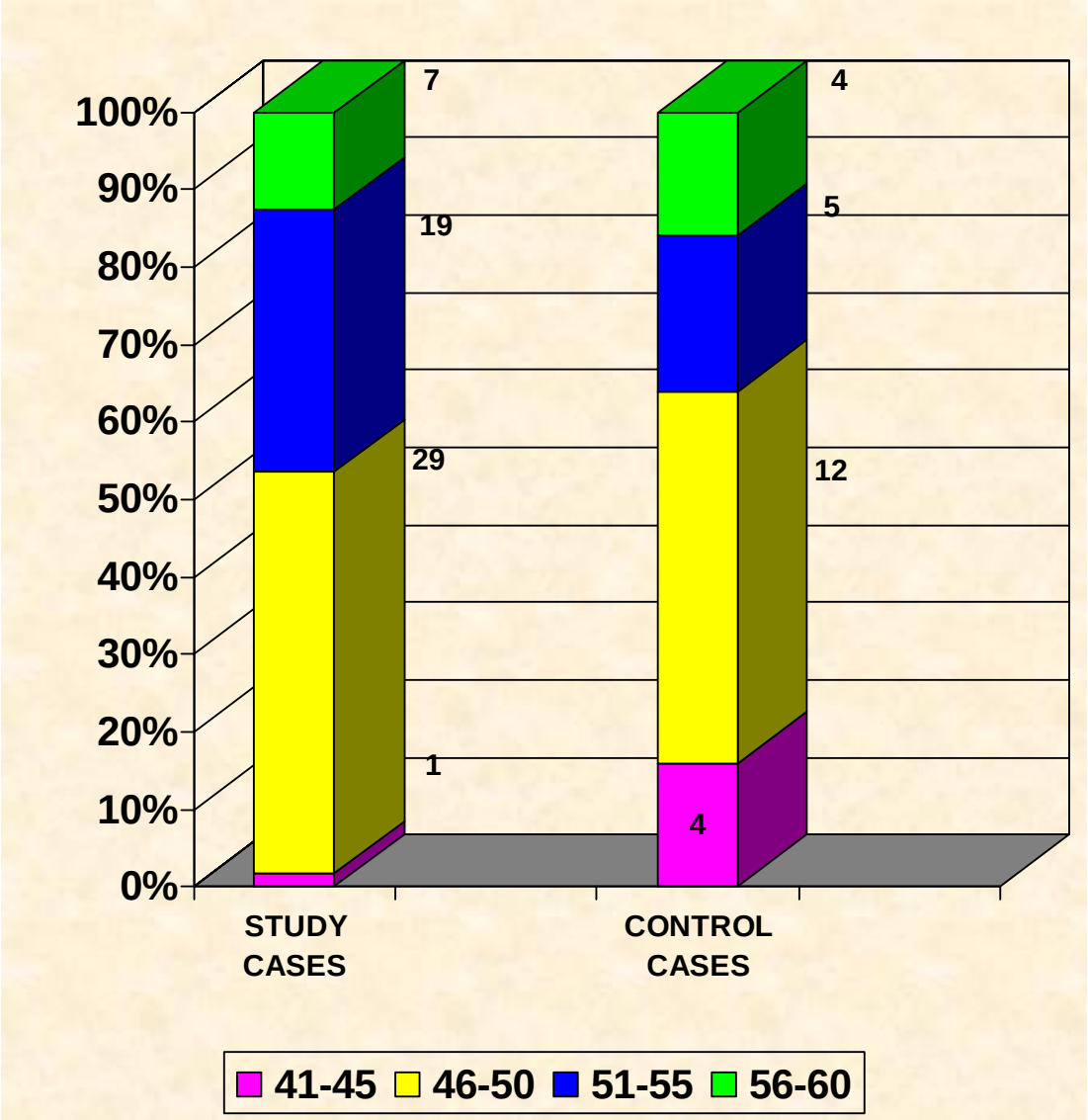
HDL - High density cholesterol (mg/dl)

LDL - Low density cholesterol (mg/dl)

TGL - Triglycerides (mg/dl)

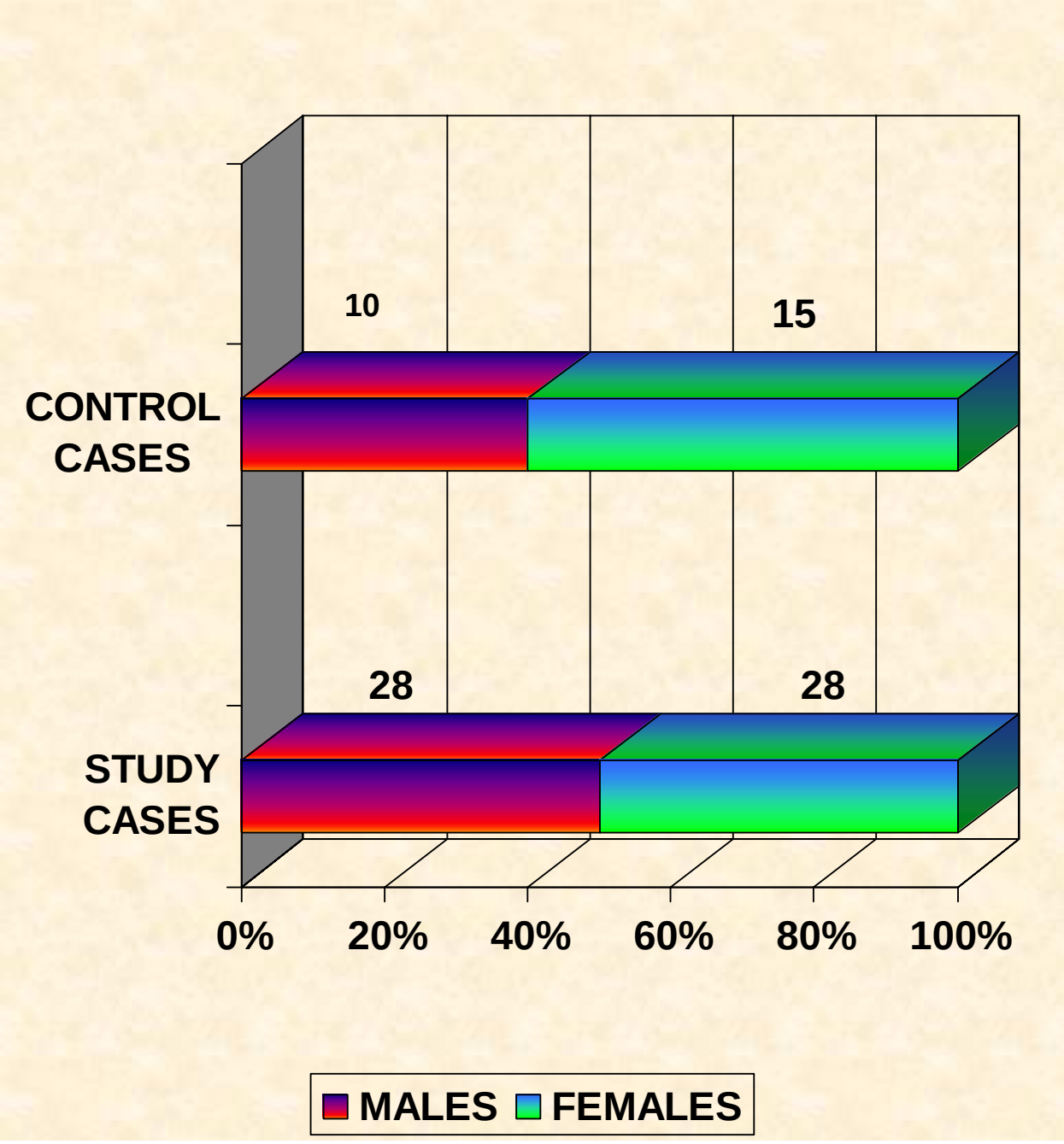
AGE DISTRIBUTION

Fig 1



SEX DISTRIBUTION

Fig 2



LIPID PROFILE

Fig 3